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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,163	12/20/2001	Sanjay Lakhotia	AM100039	1674

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EXAMINER	
FORD, VANESSA L	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,163	LAKHOTIA ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This Office action is responsive to Applicant's amendment and response filed May 19, 2005. Claims 2, 3, 5, 6, 9, 10, 14 and 16 have been amended.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

Rejections Withdrawn

3. In view of Applicant's amendments and remarks the following rejections are withdrawn:

a) Objection to the specification, page 2, paragraph 1.

b) Objection to the claims, page 2, paragraph 2.

b) Rejection of claims 1-16 under 35 U.S.C. 112, second paragraph, page 2, paragraph 3.

d) Rejection of claims 1-16 under 35 U.S.C. 102(e), pages 3-4, paragraph 4.

e) Rejection of claims 1-16 under 35 U.S.C. 102(b), pages 5-6, paragraph 5.

f) Rejection of claims 1-7 and 13-16 under 35 U.S.C. 103(a), pages 6-7, paragraph 6.

g) Rejection of claims 1-7 and 13-16 under 35 U.S.C. 103(a), pages 8-9, paragraph 7.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-16 are rejected under 35 U.S.C. 103(a) as unpatentable over van Reis *(Biotechnology and Bioengineering, Vol. 38, p. 413-422, 1991)* in view of Green et al *(U.S. Patent No. 5,780, 601, published July 14, 1998).*

Claims 1-16 are drawn to a process for extracting native or recombinantly-expressed, gram-negative outer membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Van Reis et al teach a method of industrial scale harvest of mammalian proteins by tangential flow filtration (TFF). Van Reis teach that methods such as conventional centrifugation, liquid-liquid extraction, rotary filtration offer high shear environments, slow recovery processes, high cost and the use of dead –end cartridges (pages 413-414). Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work (page 421).

Van Reis et al do not teach extracting native or recombinant inner and outer membrane proteins from bacteria.

Green et al teach a method of purifying bacteria using detergents such as Triton™ (column 4). Green et al teach that in a preferred embodiment the outer membrane components are prepared by differential solubilization of the inner membranes using Triton™ in HEPES-NaOH and $MgCl_2$. Green et al teach that a subfraction of the preparation of the outer membrane components which is rich in protein "e" (outer membrane protein P4 from *Haemphilus influenzae)* can be produced by extraction with an aqueous solution (column 4). Green et al teach that the protein "e" from the outer membrane cell wall complex can be then achieved by a two-step differential solubilization with sulfobetaine detergents (column 4). Green et al teach that the first step comprises an aqueous solution of Zwittergent™ to remove other outer membrane proteins other than protein "e" (column 4). Green et al teach that the residual insoluble components are then extracted with an aqueous solution of Zwittergent™ and this fraction results in the solubilization of protein "e"(column 4). Green et al teach that this process is performed in a homogenizer (column 14) since the instant specification teaches that a homogenizer is a microfluidizer (page 10 of the specification). Green et al teach that recombinant protein "e" can be isolated and purified by differential solubility (column 9).

It would be *prima facie* obvious at the time the invention was made to use tangential flow filtration as taught by van Reis et al to extract bacterial proteins (inner

and outer membrane) because Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work. It would be expected barring evidence to the contrary that using tangential flow filtration in a method of extracting proteins would offer high quality and high yield proteins at a low cost.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-16 are rejected under 35 U.S.C. 103(a) as unpatentable over van Reis *(Biotechnology and Bioengineering, Vol. 38, p. 413-422, 1991)* in view of Anilionis et al *(U.S. Patent No. 5098,997, published March 24, 1992)* and further view of Kolbe *(U.S. Patent No. 5,276, 141, published January 4, 1994).*

Claims 1-16 are drawn to a process for extracting native or recombinantly-expressed, gram-negative outer membrane proteins from bacteria or bacterial host cells containing a recombinant vector by differential detergent tangential flow diafiltration.

Van Reis et al teach a method of industrial scale harvest of proteins by tangential flow filtration (TFF). Van Reis teach that methods such as conventional centrifugation, liquid-liquid extraction, rotary filtration offer high shear environments, slow recovery processes, high cost and the use of dead –end cartridges (pages 413-414). Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work (page 421).

Van Reis et al do not teach extracting native or recombinant inner and outer membrane proteins from bacteria.

Anilionis al teach a method isolating and purifying of native and recombinant inner and outer membrane proteins from *Haemophilius influenzae* (columns 26-27). Anilionis et al teach that *Haemophilius influenzae* incubated in medium and centrifuged to form a cell pellet (columns 26-27). Anilionis et al teach that the cell pellet was suspended in HEPES-NaOH, EDTA and placed in a cell disruptor (columns 26-27). Anilionis et al teach that the total membrane fraction was separated into inner and outer membrane components by extraction with sarcosyl in HEPES-NaOH (column 27).

Van Reis et al and Anilionis et al do not teach divalent cations such as calcium to stabilize the outer membrane proteins.

Kolbe teaches that divalent metal ions such as calcium can form complexes with proteinaceous compounds (column 1). Kolbe teaches that divalent metal ions are

commonly used in processes of purifying proteins either as coupling agents for affinity chromatography or to precipitate proteins from liquid medium (column 1).

It would be *prima facie* obvious at the time the invention was made to add the divalent metal ions as taught by Kolbe to the process of extracting proteins by tangential flow filtration as taught by van Reis et al and Anilionis et al combined because divalent metal ions such as calcium can form complexes with proteinaceous compounds and divalent metal ions are commonly used in processes of purifying proteins. It would be expected barring evidence to the contrary, that using tangential flow filtration as in a process for extracting inner and out membrane proteins both native and recombinantly made because Van Reis et al teach that using TFF has the benefit of low shear processing, complete cell containment, high yields, potential for linear scale-up, low operating costs and the ability to use the same process for large number of products without additional development work.

Status of Claims

6. No claims are allowed.

Conclusion

7. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
August 16, 2005

NITA MINNFIELD
PRIMARY EXAMINER
8/18/05